

## General

### Guideline Title

Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the Guideline Development Subcommittee of the American Academy of Neurology.

### Bibliographic Source(s)

Armstrong MJ, Miyasaki JM. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2012 Aug 7;79(6):597-603. [31 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2015.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

1. If Huntington disease (HD) chorea requires treatment, clinicians should prescribe tetrabenazine (TBZ) (up to 100 mg/day), amantadine (300–400 mg/day), or riluzole (200 mg/day) (Level B). TBZ likely has very important antichoreic benefits, and riluzole 200 mg/day likely has moderate benefits (Level B). The degree of benefit for amantadine is unknown. Clinicians should discuss possible adverse events (AEs) with patients with HD and monitor for their occurrence, particularly parkinsonism and depression/suicidality with TBZ and elevated liver enzymes with riluzole.
2. Clinicians may prescribe nabilone for modest decreases in HD chorea (Level C), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U).
3. Whereas riluzole 200 mg/day likely decreases chorea, clinicians should not prescribe riluzole 100 mg/day for moderate short-term benefits (Level B) or for any long-term (3-year) HD antichoreic goals (Level B). Modest short-term benefits of riluzole 100 mg/day cannot be excluded.
4. Clinicians may choose not to prescribe ethyl-eicosapentaenoic acid (ethyl-EPA) (Level B), minocycline (Level B), or creatine (Level C) for very important improvements in HD chorea. Moderate antichoreic benefits cannot be excluded.
5. Clinicians may choose not to prescribe coenzyme Q10 (Level B) for moderate improvements in HD chorea. Modest antichoreic benefits cannot be excluded.

6. Data are insufficient to make recommendations regarding use of clozapine, other neuroleptics, or donepezil for HD chorea treatment (Level U).

#### Definitions:

#### Classification of Evidence Scheme for Therapeutic Interventions

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required\*:
  1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
  2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
  3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
  4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.\*\*

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

\* Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing the class is automatically downgraded to Class III.

\*\*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

#### Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)\*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

\*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

#### Clinical Algorithm(s)

None provided

## Scope

### Disease/Condition(s)

Huntington disease (HD) chorea

### Guideline Category

Diagnosis

Evaluation

Management

Treatment

### Clinical Specialty

Family Practice

Internal Medicine

Neurology

### Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

### Guideline Objective(s)

To develop an evidence-based guideline assessing pharmacologic options for treating Huntington disease (HD) chorea

### Target Population

Patients with Huntington disease

### Interventions and Practices Considered

1. Tetrabenazine
2. Amantadine
3. Riluzole
4. Nabilone

Note: The following treatments were considered but there was insufficient evidence to make recommendations concerning their use:

Clozapine, other neuroleptics, or donepezil

Ethyl-EPA, minocycline, or creatine for very important improvements in HD chorea. Moderate antichoreic benefits cannot be excluded  
Coenzyme Q10 for moderate improvements in HD chorea. Modest antichoreic benefits cannot be excluded

## Major Outcomes Considered

- Symptom control
- Quality of life
- Functional capacity
- Adverse effects of treatment

## Methodology

### Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### 2012 Guideline

MEDLINE and EMBASE searches through February 2011 performed in all languages (see appendix e-1 of the Data Supplement [see the "Availability of Companion Documents" field]) identified 424 citations. Both authors reviewed titles and abstracts for relevance and rated the resulting 33 articles using the American Academy of Neurology criteria for therapeutic classification (see appendix e-4 of the Data Supplement [see the "Availability of Companion Documents" field]).

Inclusion criteria were as follows: subjects with genetically confirmed Huntington disease (HD) or HD clinical features plus confirmed family history, a comparison group, an available pharmacologic intervention, measurement of chorea change using a validated outcome measure, and  $\geq 20$  patients. Studies with primary neuroprotective or tolerability endpoints were included if chorea was a secondary endpoint.

#### 2015 Reaffirmation

MEDLINE was searched from January 2011 to July 2015 using the search terms Huntington's disease OR Huntington chorea. Inclusion/exclusion criteria for the search included RCTs, humans only, relevant to clinical questions; criteria used to screen search results were the same as described in the 2012 published guideline.

### Number of Source Documents

33 articles using the American Academy of Neurology criteria for therapeutic classification (see appendix e-4 of the Data Supplement [see the "Availability of Companion Documents" field])

### Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

### Rating Scheme for the Strength of the Evidence

#### Classification of Evidence Scheme for Therapeutic Interventions

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required\*:
  1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
  2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
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Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.\*\*

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

\* Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing the class is automatically downgraded to Class III.

\*\*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

## Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Articles were rated according to the American Academy of Neurology (AAN) therapeutic classification of evidence scheme (see the "Rating Scheme for the Strength of the Evidence" field). Disagreements were resolved by discussion and consensus.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

### 2012 Guideline

For this evidence-based guideline, the Guideline Development Subcommittee (GDS) asked the following question: For adult patients with HD requiring symptomatic chorea therapy, what available pharmacologic agents effectively reduce chorea as measured by validated scales?

Recommendations were linked to the strength of the evidence (see the "Rating Scheme for the Strength of the Recommendations" field).

### 2015 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) member who had expertise in neurologic disease conducted a targeted

literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists.

## Rating Scheme for the Strength of the Recommendations

### Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)\*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

\*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, Neurology peer reviewers and representatives from related fields. This guideline was approved by the Guideline Development Subcommittee on November 19, 2011; by the Practice Committee on February 6, 2012; and by the AAN Board of Directors on May 14, 2012.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Safe and effective management of chorea in patients with Huntington disease

## Potential Harms

Adverse events (AEs) related to pharmacologic therapies (refer to the original guideline for drug-specific information)

## Qualifying Statements

### Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

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## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2012 Aug 7 (reaffirmed 2015 Jul 18)

## Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

## Source(s) of Funding

This guideline was developed with financial support from the American Academy of Neurology. None of the authors received reimbursement, honoraria, or stipends for their participation in development of this guideline.

## Guideline Committee

Guideline Development Subcommittee of the American Academy of Neurology

## Composition of Group That Authored the Guideline

*Guideline Authors:* Melissa J. Armstrong, MD, MSc; Janis M. Miyasaki, MD, MEd, FAAN

*Guideline Development Subcommittee (GDS) Members:* John D. England, MD, FAAN (*Chair*); Cynthia Harden, MD (*Vice-Chair*); Melissa Armstrong, MD; Eric Ashman, MD; Misha-Miroslav Backonja, MD; Richard L. Barbano, MD, PhD, FAAN; Diane Donley, MD; Terry Fife, MD, FAAN; David Gloss, MD; John J. Halperin, MD, FAAN; Cheryl Jaigobin, MD; Andres M. Kanner, MD; Jason Lazarou, MD; Steven R. Messé, MD, FAAN; David Michelson, MD; Pushpa Narayanaswami, MD, MBBS; Anne Louise Oaklander, MD, PhD, FAAN; Tamara Pringsheim, MD; Alexander Rae-Grant, MD; Michael Shevell, MD, FAAN; Theresa A. Zesiewicz, MD, FAAN; Jonathan P. Hosey, MD, FAAN (*Ex-Officio*); Stephen Ashwal, MD, FAAN (*Ex-Officio*); Deborah Hirtz, MD, FAAN (*Ex-Officio*)

## Financial Disclosures/Conflicts of Interest

### Conflicts of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and

representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at the [American Academy of Neurology Web site](#) .

### Disclosure

M. Armstrong received support as an Edmond J. Safra fellow at Toronto Western Hospital while working on this project, serves as a member of the AAN Guideline Development Subcommittee and as a Level of Evidence reviewer for Neurology®, and receives research funding from Abbott as a study subinvestigator. J. Miyasaki received grants from Medivation, NIH, and Michael J Fox Foundation; consultancy fees from Novartis for Data and Safety Monitoring and from Mertz; and speaking fees from Teva; and is a member of the Board of Directors of the American Academy of Neurology. Go to [Neurology.org](#)  for full disclosures.

## Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2015.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the [AAN Web site](#) .

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 201 Chicago Avenue South, Minneapolis, MN 55415.

## Availability of Companion Documents

The following are available:

- Evidence-based guideline update: pharmacologic treatment of chorea in Huntington disease. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Data Supplement (e-appendices, e-tables). Available from the [American Academy of Neurology \(AAN\) Web site](#) .
- Pharmacologic treatment of chorea in Huntington's disease. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology; 2012. 2 p. Available in Portable Document Format (PDF) from the [AAN Web site](#) .
- Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease. Slide presentation. St. Paul (MN): American Academy of Neurology. 2012. Available from the [AAN Web site](#) .
- Pharmacologic treatment of chorea in Huntington disease. Case presentation. St. Paul (MN): American Academy of Neurology. 2012. 6 p. Available in PDF from the [AAN Web site](#) .
- Evidence-based guideline update: pharmacologic treatment of chorea in Huntington disease. Report of the Guideline Development Subcommittee of the American Academy of Neurology. CME course. Available online to subscribers of Neurology at the [Neurology Web site](#) .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the [AAN Web site](#) .

## Patient Resources

The following is available:

- Prescription drug treatments for chorea in Huntington's disease. AAN guideline summary of evidence-based guideline for families and caregivers. St. Paul (MN): American Academy of Neurology (AAN). 2012. 3 p. Available in Portable Document Format (PDF) from the [American Academy of Neurology \(AAN\) Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

This NGC summary was completed by ECRI on November 27, 2012. The currency of the guideline was reaffirmed by the developer in July 2015 and the summary was updated by ECRI Institute on January 18, 2017.

## Copyright Statement

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## Disclaimer

### NGC Disclaimer

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